REMARKS

Claims 1-6, 8, 10-18, 20, 22-24, 26-29, and 31-34 are pending in this application. Claims 1-6, 8, 10-12, 20, 23, 26-29, and 31-34 have been amended. Claims 9, 21, 25, and 30 have been canceled. Claims 7 and 19 were previously canceled. Support for the amendments and new claims is found in the specification and claims as filed.

Claim Rejections - 35 U.S.C. § 112, first paragraph and second paragraph

Claims 25-34 have been rejected under 35 U.S.C. §112, second paragraph. Claim 25 has been canceled and its dependent claims amended to depend from pending Claim 1. Claim 30 has been canceled and its dependent claims amended to depend from pending Claim 12. Accordingly, Applicants respectfully request withdrawal of the rejection.

Claims 27-29 and 31-34 have been rejected. Claims 26 and 31 have been amended to recite that "the microcapsule comprises a gelatin microcapsule." Accordingly, Applicants respectfully request withdrawal of the rejection.

Claim Rejections - 35 U.S.C. § 103(a)

Claims 1, 4, 5, 8, 9, 12, 13, 16, 17, 20, 21, and 25-34 have been rejected under 35 U.S.C. §103(a) as obvious over WO96/10374 ("WO '374") in view of U.S. 4,919,939 ("US '939"). To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *See, e.g.,* M.P.E.P. § 2142. There is no such suggestion in any of the cited references to combine or modify the references so as to produce the claimed invention.

The pending claims are directed to a liquid adhesive for sealing a wound, the adhesive comprising a cyanoacrylate, a therapeutic agent comprising an antibiotic encapsulated in a microcapsule. In order for a cyanoacrylate-based adhesive to be suitable for use in sealing a wound, it must be capable of being applied in liquid form to the wound. As discussed in the Declaration of Yong-Hua Zhu, the majority of antibiotics contain active groups that react with cyanoacrylate, resulting in premature polymerization (i.e., solidification). Accordingly, when an unencapsulated antibiotic is added directly to a cyanoacrylate, it immediately begins to solidify,

thereby destroying the adhesive function of the cyanoacrylate, which renders the material unsuitable for use in sealing wounds.

WO '374 discloses biomedical implants that comprise a matrix material containing a porosifying agent, as well as another substance(s), such as an antibiotic. WO '374 discloses that the matrix can be a solid material that is implanted into the body, or an implant that is polymerized to solid form *in situ*. Cyanoacrylate adhesives are disclosed as an implant material that polymerizes *in situ*. However, it is not taught in WO '379 to add a microencapsulated antibiotic directly to the cyanoacrylate adhesive that is to be polymerized *in situ*. As discussed above, the direct addition of an antibiotic to a cyanoacrylate adhesive results in initiation of polymerization and solidification of the adhesive before it can be applied *in situ*.

US '939 does not offer any additional teaching over that of WO '374. US '939 merely teaches that cyanoacrylates can be used as solid matrices (*e.g.*, microcapsules) for biodegradable drug dispersions. US '939 also states that cyanoacrylates have been used as medical adhesives.

While it can be argued that both WO '374 and US '939 teach an antibiotic in a solid matrix (the solid implant of WO '374 or the microcapsule of US '939), neither reference recognizes the fact that antibiotics initiate premature polymerization of cyanoacrylates. Such premature polymerization is not a concern when solid cyanoacrylate matrices containing antibiotics are prepared, but it is a major obstacle in the preparation of cyanoacrylate adhesives containing antibiotics that maintain their liquid state until applied to a wound.

Applicants have surprisingly discovered that stable cyanoacrylate adhesive formulations that maintain their liquid state until applied to a wound can be prepared by adding antibiotic encapsulated in a microcapsule to the cyanoacrylate. The microcapsule prevents direct contact of the antibiotic and the cyanoacrylate, preventing premature polymerization of the cyanoacrylate by the antibiotic.

Neither WO '374 nor US '939 even recognizes that premature polymerization is an issue when antibiotics are mixed with a cyanoacrylate, much less teaches an effective way of overcoming this incompatibility such that a liquid adhesive for sealing a wound comprising a cyanoacrylate, a therapeutic agent comprising an antibiotic encapsulated in a microcapsule, and a defect forming agent can be prepared. A *prima facie* case of obviousness therefore cannot be made, and Applicants respectfully request that the rejection be withdrawn.

Claim Rejections - 35 U.S.C. § 103(a)

Claims 2, 3, 14, and 15 have been rejected under 35 U.S.C. §103(a) as obvious over WO '374 in view of US '939 and further in view of US 5,811,091 ("US '091").

As discussed above, WO '374 and US '939, either alone or in combination, do not teach or suggest the invention as presently claimed. US '091 includes no additional disclosure overcoming the deficiencies of WO '374 and US '939. US '939 merely teaches that butyl cyanoacrylates and octyl cyanoacrylates can be employed adhesives for sealing wounds. US '939 does not include any teachings as to preparation of a liquid adhesive for sealing a wound comprising a cyanoacrylate, a therapeutic agent comprising an antibiotic encapsulated in a microcapsule, and a defect forming agent.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claim Rejections - 35 U.S.C. § 103(a)

Claims 2, 3, 10, 11-14, 15, and 22-24 have been rejected under 35 U.S.C. §103(a) as obvious over WO '374 in view of WO96/00760 ("WO '760").

As discussed above, WO '374 does not teach or suggest the invention as presently claimed. WO '760 includes no additional disclosure overcoming the deficiencies of WO '374. WO '760 discloses biomedical adhesives comprising a biocompatible pH modifier (e.g., a microencapsulated pH modifier). WO '760 does not include any teachings as to preparation of a liquid adhesive for sealing a wound comprising a cyanoacrylate, a therapeutic agent comprising an antibiotic encapsulated in a microcapsule, and a defect forming agent.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claim Rejections - 35 U.S.C. § 103(a)

Claims 6 and 18 have been rejected under 35 U.S.C. §103(a) as obvious over WO '374 in view of WO99/20685 ("WO '685").

As discussed above, WO '374 does not teach or suggest the invention as presently claimed. WO '685 includes no additional disclosure overcoming the deficiencies of WO '374. WO '685 merely discloses coating formulations for sustained-release drug implants that include pore forming agents, but does not disclose an adhesive comprising a microencapsulated therapeutic agent in combination with a cyanoacrylate and a water soluble defect forming agent.

WO '685 does not include any teachings as to preparation of a liquid adhesive for sealing a wound comprising a cyanoacrylate, a therapeutic agent comprising an antibiotic encapsulated in a microcapsule, and a defect forming agent.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Conclusion

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns that might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number below.

Respectfully submitted,

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